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Hazards from chemicals: scientific questions and conflicts of interest

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All substances are toxic when the dose is large enough. In order to regulate the use of chemicals, we need to measure the level at which toxic effects are found. Epidemiological evidence suggests that present levels of chemical use do not lead to widespread harmful contamination of the human environment. For chemicals, most of the problems of toxicity are found in the workplace, while the population at large gets most of its toxic effects from voluntary exposure to substances such as tobacco smoke and ethanol. The prevention and control of toxic effects depends on a series of steps. This begins with measurement of toxicity in model systems, such as laboratory animals, and the estimation of the likely exposure of workers or consumers. Reliable extrapolation of information gathered from animals to the diverse and biochemically differing human population depends on understanding mechanisms of toxic effects.

The toxic effects and mechanisms of action of substances such as carbon tetrachloride or paracetamol have been extensively investigated, and our ability to predict toxicity or develop antidotes to poisoning has had some success, but epidemiology is still an essential part of assessment of toxic effects of new chemicals. The example of phenobarbitone shows how animal experiments may well lead to conclusions which do not apply to man. After measurement of toxicity and assessment of likely hazards in use comes the final evaluation of the use of a chemical. This depends not only on its toxicity, but also on its usefulness. The direct effects on health may be small in comparison with the indirect advantageous effects which a useful substance such as vinyl chloride may bring.

The assessment of risks and benefits of new chemicals can be partly removed from a political style of discourse, but the evaluation of the relative weight to be attached to these risks and benefits is inescapably political. The scientific contribution must be to allow the debate to take place in the light of maximum clarity of information about the consequences of use of chemicals.

Introduction

Modern societies depend on the extraction, manufacture and use of materials ranging from natural products such as asbestos or coal to synthetic organic compounds like vinyl chloride, unknown in nature. The scale of use and transport varies from millions of tonnes of petroleum hydrocarbons and chlorine, to a few

tonnes of insecticides and kilograms of drugs and food colours (Korte 1977). These diverse substances form a new chemical environment for man. The possibility that they may have adverse effects on the human populations and the natural environment, not previously exposed to the materials, has gradually become part of public consciousness (Carson 1963; Kates 1978; Jones *et al.* 1978; Royal Commission on Environmental Pollution 1976). The question is: how can we evolve a system that deals with the new dangers of this new environment, while retaining the more beneficial aspects of technology?

It is best to separate out these political and scientific questions into their component parts (Lundqvist 1977; Gregory 1971). Is there evidence of harm from industrial chemicals now? How can we examine new chemicals to predict what effects their future use would bring? What institutions can we set up to decine whether and how to use new chemicals?

Social and chemical factors in the cause of disease

There is massive evidence that many chemicals used in industry have serious long-term toxic effects on some workers in industry, and that strenuous and continued efforts are required to reduce exposure of workers to toxic chemicals (see Hunter (1975) or any issue of the *British Journal of Industrial Medicine*).

The pulmonary diseases of asbestos workers and the increased risks of mental impairment or death from coronary heart disease among rayon workers exposed to CS_2 are two examples among very many (Elmes & Simpson 1977; Hänninen 1971; Tiller *et al.* 1968). It is difficult to assess the scale of injury, because industrial workers are not a random cross section of the population, but are markedly healthier than average at the time of entry to work, so that survival, illness and disability will depend on the kind of person who enters the industry as well as the conditions of work (Fox & Collier 1977). However, mortality among most occupational groups seems more related to social class than to the particular materials that are handled at work. For instance, unskilled workers in the various industries from catering to chemicals do not have greatly differing mortalities, though they are all high in comparison with skilled or professional workers (Registrar General 1971, 1978). This may reflect generally dusty, cold or wet conditions of work and life, or reflect a way of organizing living conditions that is not conducive to longevity (Knowles 1977; Belloc 1973; Brown & Harris 1978; Brown *et al.* 1975). When the survival of the wives and children as well as men at work is considered, it becomes clear that there is a steep social gradient of mortality and presumably morbidity, most of which cannot be due to exposure to the chemicals found in the workplace (tables 1 and 2). Table 1 shows that almost a third of warehousemen die in the 20 years before reaching retirement age. In this and in the causes of death they are typical of the general population (standardized mortality ratio (s.m.r.) 104 instead of 100). Of this group 12% will die of lung cancers, one might say, voluntarily. They differ markedly from teachers

who have almost halved their mortality in the age range 45–64 years. Both the leukaemia s.m.rs are close to the expected 100 value, showing that there are unlikely to be gross errors of estimate of population size.

TABLE 1. MORTALITY AMONG TEACHERS, WAREHOUSEMEN AND THEIR WIVES

(Deaths per annum per 100000 persons.)

age	teachers (wives)	warehousemen (wives)
25–34	73 (48)	115 (57)
35–44	135 (106)	248 (155)
45–54	414 (277)	771 (381)
55–64	1297 (617)	2223 (973)
	standardized mortality ratios	
all deaths	60 (66)	104 (98)
leukaemia	102 (64)	93 (90)
lung cancer	34 (64)	107 (101)
coronary heart disease	80 (60)	110 (96)

From Registrar General (1971), tables 3Aii and 3Bii; International Classification of Occupation nos. 287 and 210.

TABLE 2. INFANT MORTALITY 1972

(Deaths per annum per 1000 live births.)

London		Hampshire (rural)	14
Tower Hamlets	26	Hampshire (Portsmouth)	15
Lambeth	19	Anglesey	22
Camden	15	Yorkshire (towns)	21
Sutton	13	Yorkshire (rural)	19

From Registrar General (1974), table 13.

The wives of teachers and of warehousemen have lower mortality rates than their husbands, but again show a strong social gradient. Table 2 shows that infant mortality is high in the poor areas of London (Tower Hamlets and Lambeth) while Camden, being more prosperous and with an unusual concentration of major hospitals and paediatric services, does better in spite of being in the central area of the town. The other figures also suggest that prosperity and good health services are the important shields against death in infancy.

The Study Group on Long-term Toxic Effects to Man from Man-made Chemicals was set up in 1975 to consider the question whether there was any widespread danger to people from chemicals in the environment. The answers seem to be that there are localized patches of harmful pollution, such as areas with excessive lead in the drinking water in parts of Scotland, excessive dust and sulphur dioxide in the atmosphere in some towns, and asbestos dust outside factories, but that there was no evidence of present widespread danger to health from environmental pollution, outside the workplace.

We look at public health records and we see that almost 30% of men die between the ages of 45 and 64 years, and that the incidence of a number of cancers and other serious diseases is not falling. There is powerful evidence that the major differences in disease and mortality between nations and between social classes are environmentally and socially determined and are not genetic in origin. The question is then forced on us: what aspect of our environment causes these differences in disease incidence?

The major causes of premature death are accidents, coronary heart disease, and the cancers. The present role of specific man-made chemicals in the causation of these ills seems to be a minor one, since the variation between town and country, and between occupational groups of similar social standing but handling different materials, are, with minor exceptions, small. The major differences between groups seem to be largely accounted for on the basis of differences in cigarette consumption, exercise, diet and all of the socially determined living conditions, from overcrowding to the availability of bathrooms (Registrar General 1978; Brown & Harris 1978).

We still need to investigate specific chemicals, by using the techniques of clinical observation, epidemiology and toxicology to measure effects of chemicals in use, and in particular we need to prevent future errors such as the introduction of cigarettes some 70 years ago.

In addition, the occupational and accidental hazards from exposure of relatively small groups of people to reactive chemicals are likely to increase. Such groups of a few hundred people per group will be too small for most epidemiological work, and we will depend on the accuracy of our predictions of toxicity before human exposure takes place.

One of the first steps is to try to predict whether the 500 or so new chemical compounds that are brought into commercial use each year are likely to have harmful effects, and to investigate those existing chemicals about which there is suspicion.

Present methods of control of new chemicals and prediction of adverse effects in use

When a manufacturing company develops a new compound, say an insecticide to control carrot fly, this is done on the basis that there is a need for the product and a possible market that will justify the expenditure of resources in development (but see Galbraith (1975) on creation of needs). Before the material can be applied to a crop, even on an experimental basis, clearance from the controlling committee is requested (in the U.K. the scientific subcommittee of the Pesticide Safety Precautions Scheme at the Ministry of Agriculture, Fisheries and Food would be approached; M.A.F.F. 1971).

All substances are toxic, given a sufficient dose. To ask 'is this substance toxic?' is not the right question: oxygen, water or vitamin D are toxic. Toxicity

is a property of materials, like density. The question that we need to ask is whether there is risk attached to the use of a material, and this will depend on the quantitative and qualitative aspects of the toxicity of the material and its particular use.

We can measure toxicity in model systems, and by epidemiological techniques. When our hypothetical insecticide is presented to regulatory committees it has already a file of 'toxicity data' of perhaps 1000 pages.

TABLE 3. A GENERAL STRATEGY FOR ASSESSMENT OF RISKS FROM NEW CHEMICALS

1. Toxicity: measured in model systems.
2. Risk assessment: from toxicity measurements and exposure estimates.
3. Risk: evaluation from assessments of risk and benefit and the alternatives available.
4. Epidemiological: surveillance to guard against unsuspected risks and as verification of evaluation procedures.
5. Responsibility and resources for safe handling assigned.
6. Reiteration of steps 1–5 in light of experience. Each step is considered for (*a*) worker, (*b*) environment, (*c*) consumer.

TABLE 4. HEALTH AND SAFETY COMMISSION PROPOSALS

(Part of proposed minimal list of information to be requested by Health and Safety Executive for registration of all new chemicals.)

1. Chemical and physical properties
2. Biological properties:
   acute oral or inhalation toxicity;
   eye and skin irritancy;
   results of short tests for carcinogenicity, mutagenicity and teratogenicity;
   subacute toxicity (30 days);
   biodegradability;
   fish toxicity.

(From Health and Safety Commission 1977.)

The effects of single and multiple doses, given by various routes (to various species of animals), will be described. The teratogenic, mutagenic and carcinogenic potential of the chemicals will have been investigated, together with effects on skin and eye, on birds, bees and fish, on reproduction and on bacteria. The metabolism, excretion, and perhaps mode of action of the compound will be presented. All this is usually done at dose levels far higher than the doses to which operatives or consumers will be exposed. The doses are designed to demonstrate what kind of toxicity the compound displays, which tissue is affected, and what functions altered. The mass of information is presented, together with much other material, to a committee of medical, agricultural and wildlife specialists who may ask for more investigations to be done (M.A.F.F. 1971).

From this array of experimental results on model systems emerges a general picture of the ability of the compound to cause harm to living organisms. In

particularly, the dose–response relation for different effects is observed. The compound can then be compared with other compounds of similar structure, or similar action, whose effects on man and environment are known from previous use, or often from previous misuse and regretted ill-effects.

Given our assessment of the toxicity of the new compound (tables 3 and 4), we then look at the proposed use, and the estimated exposure of different groups of people such as agricultural workers inhaling the spray, or consumers eating residues on food. From the dose predicted for man and from the effects on model systems we make predictions of what is likely to happen in use. At this stage it is possible to make an evaluation, a value judgement, of whether the benefits make the risks acceptable.

In essence and to a variable extent, some such procedure is followed for new drugs, pesticides and food additives, and will soon have to be followed for all new industrial chemicals (Health and Safety Commission 1977; D.H.S.S. 1977) The ability to predict whether a new substance will cause harm in use is imperfect. First, there are massive variations in the way that different species and different individuals respond even to the same measured dose of a compound. The calculated dose to which man is exposed rarely takes into account inter-individual variations of dose due to variation in behaviour. A lady who eats 1 kg of carrots per day recently appeared in hospital because of the yellow colour of her skin, from carotene, not from pesticide residues. Should we allow for such individuals? No one would have predicted that some men would smoke 80 cigarettes per day when these were first marketed, nor that some individuals would take kilograms of phenacetin headache powders. We need information on the extent to which instructions to wear protective clothing when spraying insecticides are complied with.

Another major difficulty comes from accidental, improper, or even illegal use of new substances. Insecticides spilt in railway wagons have contaminated sacks of flour. Jet engine oil has been used to adulterate cooking oil, and dangerous materials are frequently used improperly in the factory or farm (McLean 1972; Jones *et al.* 1978; Mark & Stuart 1977; Rycroft *et al.* 1976; Smith & Spalding 1959).

Lastly, we have the problem of prediction of the effect of a substance such as a food colour on large numbers of individuals, perhaps millions, when we have a dose–response curve from animal models or human studies, where at the most only a few hundred individuals were observed.

This last question is particularly disquieting where we have an 'all or none' type of effect and the response is measured in terms of probability of effect versus dose of substance. This is so for induction of cancer by chemicals and leads to a difficult calculation of low probability multiplied by large numbers of persons exposed.

Because of the difficulties of prediction of 'safety in use', the large number of new drugs and industrial and agricultural chemicals being developed, and short-

age of toxicologists, many regulatory authorities and industrial scientists have tried to set down a detailed scheme of tests for the assessment of toxicity of new chemicals. If a set of tests could be prescribed, then the developer firm need only carry out the work on the prescribed list, and the regulatory authority can tick off the results on a check list. The process of 'toxicity testing' would become a simple predictable routine, with a predictable cost and time course for any new compound. Unfortunately, it seems impossible to devise a set scheme which will give us the information we need. We can only give general principles of investigation, and make a balance between laboratory studies before use and surveillance of exposed populations after use has begun (M.A.F.F. 1971; D.H.S.S. 1977).

Since an infinite number of investigations are possible, it is necessary to decide which of these are relevant in the light of the nature and intended use of the chemical. It is like the investigation of a new disease. No routine set of steps, no rigid guidelines of investigation can be laid down for the investigator, except for the very minimum that needs to be done. For instance, the acute toxicity to mammals in terms of lethal dose, and organ affected, should be known. Some estimate of persistence in biological systems, mutagenicity, and effects of repeated exposure will be needed. But depending on the results of the first investigations, the next steps must be designed to lead to elucidation of mechanisms. The alternative way of 'routine' investigation already leads to massive, uninformative, wasteful, and misleading 'toxicity tests'. The quality of the investigation falls and scientists of imagination, needed to solve new problems of new chemicals, are discouraged from this field.

Mechanisms of toxicity and extrapolation to man

If we know the way in which a new toxic material penetrates metabolic paths and the molecular targets with which the toxic reacts, to cause injury, we are then able to use our knowledge of the biochemistry and physiology of any species to predict responses to the new toxic material. In contrast, the crude and mechanical description of, say, lethal effects in one species will tell us little about other species, or about variation inside a species. Human populations have great genetic diversity, contain individuals of different ages and states of health, living in a wide variety of environments. In particular human diets vary greatly, especially in regard to the amount and type of foods eaten. How can we take these factors into account?

Examples: paracetamol and carbon tetrachloride

The drug paracetamol (*N*-acetyl-*p*-aminophenol) is a useful analgesic, but causes liver necrosis and death in rats or man when taken in overdoses of from 20 to 100 times the normal dose. The question can be asked; is this an adequate safety margin, or will some individuals be sensitive to normal or repeated doses?

The drug is well absorbed, and is normally removed harmlessly after conjugation in the liver to a glucuronide or sulphate. Toxicity depends on a second pathway of metabolism by drug oxidizing enzymes centred on cytochrome P450 in the endoplasmic reticulum of the liver cell. A reactive metabolite, probably *N*-hydroxyparacetamol, is formed, and combines with glutathione. As the liver reserves of glutathione fall, so the metabolite attacks other cell components and cell death results. Treatment with inducers of synthesis of the cytochrome P450 enzymes, such as DDT or phenobarbital, or treatment with low protein diets that reduce liver glutathione content, make animals sensitive to paracetamol (Mitchell *et al.* 1975; McLean & Day 1975).

TABLE 5. THE EFFECT OF DIET AND PHENOBARBITAL TREATMENT ON LIVER CELL COMPOSITION ON THE LETHAL EFFECTS OF PARACETAMOL AND CARBON TETRACHLORIDE IN RATS

diet	phenobarbital treatment	liver glutathione (μmol/g liver)	liver cytochrome P450 (nmol/g liver)	l.d.$_{50}$, paracetamol (g/kg)	l.d.$_{50}$, CCl_4 (ml/kg)
stock	–	6.9 ± 1.7	40 ± 9	5.2	3.6
low protein	–	2.2 ± 0.2	23 ± 5	2.1	14.7
stock	+	7.6 ± 0.1	142 ± 35	2.0	0.5
low protein	+	2.8 ± 0.3	81 ± 15	0.9	1.4

(Data from McLean & McLean (1966), Garner & McLean (1969), McLean & Day (1975) and unpublished results.)

Knowing the normal range of variation of cytochrome P450 and glutathione content of human liver, and from epidemiological studies of overdose, and making reasonable assumptions about rates of synthesis of glutathione and the range of dietary protein intake, we can say that the usual 1 g dose of paracetamol will not cause liver damage to any member of the population even if repeated at 4–6 h intervals, and even if used in a developing country. However, we can never rule out the possibility that a genetic variant may exist where differences in metabolism or immune systems cause individual sensitivity to this or any other chemical.

In contrast to paracetamol, laboratory investigations on the relation of diet to toxicity of carbon tetrachloride (CCl_4) showed that toxicity and glutathione levels were not related, but the amount of tissue injury and lethal effects produced by a dose of CCl_4 were directly proportional to P450 levels in the liver (table 5). We can conclude that the toxic metabolite of CCl_4 is not detoxicated by glutathione and it is worth considering whether the metabolite exerts its effects entirely in the lipid phase of the cell.

By altering the chemical environment of an animal we alter its cell composition in an adaptive manner; this in turn can alter response to toxic materials, by an order of magnitude. The conclusion that one may draw from experiments of this

kind is that the assessment of the toxicity of a compound, based on the effects of exposure of healthy laboratory animals fed stock diets, is a very limited assessment. If we can improve our understanding of mechanism, then our extrapolations become more confident; the use of methionine in therapy of paracetamol poisoning was based on such experiments (McLean 1974). Human epidemiology remains a necessity for rational control of potentially toxic chemicals, because we cannot extrapolate with certainty from animal models.

Epidemiology to verify toxicity assessment

In man, acute exposure to CCl_4 leads more often to renal injury than liver damage. The kidney also contains enzymes linked to cytochrome P450, but the reason for the distribution of injury between liver and kidney in rat and man is unknown.

Even when we do have a reasonable idea of a mechanism of toxicity, we still have to monitor the effects of human exposure to new chemicals.

Without such studies on man, we can never verify the correctness of our techniques of measuring toxicity in model systems. We may be using quite inappropriate models and unless we correct our techniques we could go into an irrational system of regulations. Chemicals that cause mutations in bacteria or *Drosophila* are used in many industrial processes. There are no known instances of increased mutations in the offspring of persons exposed to mutagenic chemicals. Even though this is a negative finding whose reliability depends entirely on how many people are examined, such knowledge is the only way of providing a sense of perspective for judging the relative importance of regulations against mutagenic chemicals (except in so far as they may also pose carcinogenic hazards) versus regulations designed to reduce acute poisoning of persons using insecticides, or, say, road accidents. In dealing with toxic chemicals, errors that underestimate risks will injure workers, consumers or environment. Errors that overestimate risks will also cause damage because the unnecessary abandonment of, say, a new drug will lead to loss of the expected benefits, and may lead to the loss of the research and development costs. The loss of great investments of time and materials will eventually be spread over the society, and make resources unavailable for other objectives (Westlake 1977).

The required epidemiological work can take two forms. First, there can be surveillance of the physical and mental health of the exposed and control populations with the use of questionnaires and general practice records. Secondly, there can be specific surveys relating to items of suspicion, perhaps to fears that some specific tissue will be injured, arising from toxicity data. For instance, liver function tests might be carried out in an exposed population.

Phenobarbital and the wrong model system

In assessing the potential of a compound to cause cancer in man, we rely largely on animal experiments where large doses of the compound are fed to rats or mice.

The class of substances that induce synthesis of cytochrome P450 and the associated drug metabolizing enzymes in the liver of most mammals includes phenobarbital, DDT, and many other drugs and chemicals, some of which occur naturally. Some of these are powerful inducers, causing an increase in liver mass and cell number as well as an increase in size of the hepatocytes. Long-term feeding with phenobarbital or DDT leads to an increased incidence of liver tumours in some strains of mice and rats, and some of these tumours are malignant. There is no doubt that for certain strains of mice phenobarbital is a carcinogen. The question is whether the classification of compounds into 'carcinogens' and 'non-carcinogens' is a rational classification, or whether it is a misleading over-simplification. The development of a tumour depends on multiple factors in the host and the environment (Anon. 1974) and several of these factors are necessary but not sufficient causes. For instance, high protein and high fat diets cause a marked increase in incidence of both spontaneous and carcinogen-induced tumours. If all inducers of microsomal enzymes are to be called carcinogens, we have to face the fact that many natural compounds and many pesticides and drugs are inducers, and that increasing the dietary protein and fat content has similar effects.

The discussion is made more intense and more difficult by the observation that phenobarbital treatment can protect against the carcinogenic effects of aflatoxin on rat liver (McLean & Marshall 1971) and that two economically important insecticides, aldrin and dieldrin, seem to produce liver tumours by the 'induction' type of mechanism.

It becomes important to decide whether the human liver is like the mouse liver in its response to inducing substances, and since no mechanism for the carcinogenic effect in the mouse has been discovered, we have no theoretical basis in which to work.

However, we are fortunate to have a large human population to study, since phenobarbital has been used as an anti-epileptic drug for over 40 years (Clemmesen *et al.* 1974).

Studies in Denmark and in London have shown no excess of liver tumours among patients with epilepsy (table 6). The incidence of liver cancer in the general population of England and Wales is very small (28 per million in men aged 55–64 years, in comparison with 2900 per million for lung cancers, or an estimated rate of 1070 for liver cancer in an area of Mozambique in which food is heavily contaminated with aflatoxin) (Van Rensburg *et al.* 1974), and in any sample there is the possibility of missing the patients who have the tumours. In our sample there is a 7% probability that we would miss even an eightfold increase of liver cancer incidence. However, such an increase would still make the

risk from liver cancer negligibly small in comparison with the risks of death from untreated epilepsy, with the risks from cigarette smoking, or with the benefits from the use of phenobarbital.

Since phenobarbital acts as an effective inducer of P450 synthesis only on liver tissue, we can say that any carcinogenic risk to man from this whole class of substance is unlikely to affect other tissues and is very small in comparison with the normal risks of living. The model system of tumours in the mouse liver has probably given a false positive signal, while the studies on patients with epilepsy lead us to look at other factors that cause the high observed mortality.

TABLE 6. MORTALITY IN 2000 PATIENTS WITH SEVERE EPILEPSY (CHALFONT CENTRE), 1951–77

	observed	expected	O/E	95 % confidence limits for O/E
deaths, all causes	636	208	3.1	2.8–3.3
liver cancer	1	0.6	1.5	0.0–8.5
accidents	64	14.6	4.4	3.3–5.6
epilepsy (mostly status epilepticus)	207	2.7	75.8	65.7–87.0
cancer, all sites	73	51.6	1.5	1.2–1.9
lung cancer	23	16.3	1.4	0.9–2.1

(Study by S. White & A. McLean, manuscript in preparation.)

There are many other technical problems in the assessment of toxicity of chemicals. There is difficulty in detecting the potential for renal toxicity and bone marrow toxicity. The ability of a compound to produce skin sensitization and other allergic diseases in man is hard to assess from investigations in animals.

Each new investigative technique poses difficulties of interpretation. For instance, practolol metabolites seem to bind to proteins and so act as haptenes in producing an immune reaction. The relation of such an immunological effect to the disastrous side effects of practolol is unknown, so we cannot use the technique to investigate new compounds with any confidence (Amos *et al.* 1978).

Each new technique has to be applied to a large series of compounds which have already been used, so that we can see whether, say, metabolite binding to plasma proteins correlates with delayed side effects, or whether it is an incidental event of no consequence and no utility in the investigation of new compounds.

These are questions of the design and interpretation of experiments to investigate the toxic effects of new compounds. There are other questions of equal importance concerning the design of institutions and procedures to control the use of toxic chemicals.

Conflicts in the perception and control of risks

We cannot eliminate or even detect all of the risks to life and health that come to workers in their workplace, or to consumers in their use of products. This is first because every single substance carries risk in its manufacture and use, from drowning in beer and cancer from asbestos to falling from household ladders. Secondly, we can detect only those events that are sufficiently noticeable or frequent to show up in studies on exposed and control populations. Sensitivity to a chemical due to a rare metabolic pathway would not show up in human or in animal studies unless it caused a bizarre illness.

Our present model systems for assessing risks or benefits do not give us sufficiently precise answers for us to be able to predict the effects on quality of life of the introduction of a new product, or consequences of a ban on use of an old chemical. A new drug might be a minor advance or a major disaster. Stringent controls on a chemical such as benzene may save lives at a huge cost to the community, or may save no lives but lead to improved production and management methods, or any combination of effects (Westlake 1977).

Since all processes and products carry risk it is no great advance to say that we must permit only acceptable risks. The questions are: what is an acceptable risk, and who decides on its acceptance?

No expert is ever at a loss for more tests that he thinks could be done to define the toxicity of a chemical. The protection of the environment and prevention of risks to health of workers and consumers are put forward as an absolute, good, and sufficient reason for more testing and more precautions. Each expert presses the urgent need for work in his own field, be it neurotoxicity, cancer, mutagenesis or damage to bees.

In committee one sometimes gets the feeling that no one without a degree in toxicology should be allowed to take a bath lest there be a side effect damaging health or environment.

Meanwhile there are groups in industry who seem incredulous at the idea that any product they make could ever do any significant harm, and see no need for government committees to do anything except endorse the safety of their products.

Outside these official circles are critics who say that testing is inadequate, companies venal, committees ignorant and corrupted (Kinnersley 1974; Gillespie *et al.* 1978; McLean 1978).

We could spend a large proportion of the national product on protection of the environment and safety testing procedures, but might rapidly reach the point where the loss of production and lowered living standards depressed health far more than any gain coming from increased knowledge about toxicity.

There are several conflicting interests involved in the process of deciding how much of the society's resources should be devoted to ensuring safety and who should pay. The conflicting interests of owners of enterprises and the workers who carry risks are obvious, but need to be resolved. Making available the best

scientific information to both parties may help. Certainly secrecy has no proper place in the field of toxicology, for only by open disclosure of toxicity data and risk estimates can proper evaluation take place (Smith 1977).

Government action to ensure that all enterprises have to comply with the same proper safety standards will help to ensure that managers are less tempted to secure competitive advantage by skimping safety costs.

The conflicts over distribution of advantages gained by new economic processes between worker, management, owners and the rest of society also spill over into discussion on safety. The interests of the rest of society can appear to be contrary to those of the workers in a particular industry. For instance, there are over 150 accidental deaths per year on building sites in the U.K. (H.M. Chief Inspector of Factories 1974). The better safety standards that ought to be imposed would raise building costs, as well as requiring a bigger inspectorate to oversee the sites. One could argue that the major source of improvement in public health has been improved living standards, in the form of better housing, food, and social services. These benefits are possible because of increased productivity of labour, and if increased efforts in the direction of safety are misplaced, then the health advantages made possible by resources created by a new technology would be lost.

At times it may be right and necessary for social reasons to incur safety costs that are not cost effective in comparison with investment in some other health field. For instance, the cost of bringing vinyl chloride monomer concentrations down from about 20 parts/10^6 to 4 parts/10^6 or less, at a cost of about £10000 per exposed man, will probably be far less effective in saving life than a similar sum spent on the more dangerous building sites (Lassiter 1977). However, the known carcinogenic risk, although much less than that posed by cigarettes, is regarded as intolerable perhaps because it is insidious and incurred at work, and so regarded as a risk imposed by management rather than undertaken voluntarily. The economic impact of improved safety regulations and their enforcement, onto general living standards should be studied. It is possible that increased attention to safety would improve managerial involvement and improve industrial relations if correctly planned. Just as we have a budget for the national health services inside which we try to allocate resources, so we need to decide on a budget for environmental quality and risk avoidance. Inside this broad field we could allocate resources to specific areas, like noise in industry, or risk assessment of new drugs. Unlike health service expenditure, which is centrally funded, much of the allocation of resources on safety comes in the form of requests by government committees that someone else, usually industry, should spend money, find and train people, or feed and examine a few thousand rats. Such requests do not appear on the public expenditure bill, but are still allocations of resource and perhaps it is time that we acknowledged that these resources are limited.

This proposal, of making a budget for risk avoidance, poses considerable difficulties, but so does the present alternative, where only informal commonsense stands in the way of an infinite expansion of requirements for testing of chemicals,

drugs and pesticides. We could start by taking one field, say the evaluation of food additives, and making a budget to allocate expenditure between animal tests, and observations on human populations. It is doubtful whether the present division of resources in research on, say, nitrosamines in food would still be heavily biased towards rat experiments if such a budgeting procedure were followed.

Acceptable risk

The concept of acceptable risk is currently much discussed (Lowrance 1976; Starr 1969; Starr *et al.* 1976; Kletz 1976, 1977; Ashby 1976; Pochin 1975; Farmer 1975, 1977; Fairclough 1977; Council for Science and Society 1976, 1977). Acceptable risk is not definable as a particular quantity. People undertake voluntarily the high risks of cigarette smoking, rock climbing, or driving motor cars. At the same time, involuntary risks imposed by lead in petrol or food additives are accepted only reluctantly and only if the risk can be described as unmeasurably small. The risks at work seem to be more intolerable if due to a chemical with carcinogenic or other insidious toxic effects, than if the risk is posed by a visible feature such as the danger of falling from scaffolding. Similarly, surgical risks are accepted more readily than medical risks (Glaser 1977). Certainly the pressure for regulation of chemical hazards seems far greater than the pressure against causes of mechanical trauma, which may be just as much a cause of permanent disability (Kinnersley 1974). The distinction may lie not in the magnitude of the hazards but in the objections which people have to being controlled and used by other persons. So, lead in the air is regarded as an imposition on the public by the actions of motorists and oil firms, while nitrate in drinking water, present in amounts closer to toxic levels, is regarded with equanimity perhaps as a natural consequence of agriculture. Drug toxicity is often regarded as intolerable. Acceptability of risks is essentially a political problem of accommodation between different groups in the society, with separate interests, depending on occupation, age, education and many other factors.

The perception of risks is frequently inaccurate (Abelson 1977; Slovic *et al.* 1976) and again depends on social factors, so farmers and scientists working in pesticide manufacture see the balance of risk and benefit from pesticide use quite differently from the way in which independent pesticide specialists and wildlife specialists see those same benefits and risks (Davis 1978).

An accident in which six people are killed at once is regarded as 'newsworthy' and more serious than six separate fatal accidents, or the background figure of 15 motor traffic deaths per day in the U.K. Perhaps this reflects the more serious social consequences of multiple deaths in one family or community, in comparison with separate events spread over many social groups. Similarly, 300 men each off work for 1 day because of minor illnesses are quite different from one man losing 300 work days, so adverse effects cannot be reduced to a simple currency of days off work.

Joshua Lederberg (1974) pointed to the social loss implied in setting the risk levels so low that new compounds are not developed and that the effort expended in examining new compounds should be rationally examined and set to produce a benefit:cost ratio that is socially acceptable.

The University of Sussex group have suggested that safety costs were unevenly distributed between industries, but make the assumption that such costs are direct costs of production without any benefit to management or to productivity. When the costs of air-conditioning are treated as 'safety costs' the argument becomes dubious (Sinclair *et al.* 1972).

The Science Council of Canada (1977) has taken the discussion further than other groups, and sees the key to the problem as being informed discussion between the representatives of the major groups, consumer, worker, and management, leading to agreement on action to be taken. It is becoming clear that no experts can decide what is an 'acceptable' risk. Expert groups can only decide what the risks are.

The Science Council recommends the setting up of a unified 'Advisory Council on Occupational and Environmental Health'. This body would have the responsibility to commission research to define hazards, and then to set in motion procedures to control the hazards.

In the U.K., the plans put forward by the Health and Safety Executive propose that when considering new chemicals in their industrial aspects, trade union representatives should be consulted. But frequently the consumer's voice is also needed when arrangements are being made between the large organized bodies, departments of government, manufacturing firms and trade unions. For instance, many consumer products such as wood preservatives, over-the-counter medicines, or the caustic soda used to clear drains, are hazardous if used carelessly, as are paraffin oil, matches, or axes. The temptation is for official bodies to restrict the use of any substance to which a hazard can be attached, to some professional licensed group. So some timber preservatives are on sale only to specialist firms. Since everyday life has hazards, we should recognize some chemicals as posing risks of only average severity which do not increase the overall risks to life by an appreciable amount and permit their use in the household, provided that adequate labels are supplied.

It has become clear that our increasing ability to analyse information about mortality and disease gives us new power to detect risks. New analytical methods enable us to detect environmental contamination, new toxicological methods allow us to infer that hazards of carcinogenesis, teratogenesis and other tissue injury are associated with particular chemicals.

We are unable to guarantee safety of new drugs or other chemicals, but the demand for safety grows together with the demand for new products. At the same time, 'voluntary' risks, such as those posed by cigarette smoking, driving motor vehicles, or inactivity are responsible for a high proportion, perhaps half, of all deaths before retirement. We are unwilling to discontinue the use of all

hazardous chemicals, because of the drastic decrease in consumption that this would involve. Since we accept the use of toxic chemicals knowing that they present a risk, what conditions should we make before permitting them? Table 7 puts forward a suggested list.

TABLE 7

A risk to life and health is unacceptable unless it is minimized, or if unavoidable, equitably spread through society.

Except for risks that are:

(1) voluntary, not imposed;
(2) known, not concealed;
(3) benefit is shared by the risk taker and society;
(4) information on consequences of risk is measured and made public to reduce further risk.

In the cases of deep sea fishing, immunization of children, or vinyl chloride polymerization, the conditions for 'voluntary risk' are now more or less fulfilled. With cigarette smoking the question of benefit and cost is more doubtful, since the cost to society may be much larger than current benefits (Atkinson & Townsend 1977). For food additives and colours and pesticide residues in food, the element of concealment and lack of any epidemiological surveillance makes the present style of use doubtful.

LEGAL RESPONSIBILITY

A further step is to assign responsibility for management of toxic chemicals.

Societies regard certain commodities as precious or dangerous and set aside particular individuals and procedures to guard these substances. Explosives, morphine, radioactive substances, gold or money fall into this category (Council for Science and Society 1977).

In each case there is a dosage factor: small amounts are permitted for personal use, from coins to percussion caps or luminous watch dials. Larger amounts are in the care of responsible individuals, such as accountants or hospital physicists, who have to account for the proper handling and disposal of money and radioisotopes respectively. Perhaps we need toxic substance managers who are qualified to accept delivery of designated toxic substances, and are held responsible for safe disposal. Almost any substance can be dangerous, as even flour dust can explode. The problem is to combine knowledge of toxicity, perception of hazard, and motivation to carry out proper management. The scientists' task is to obtain and organize the information about risk so that it becomes accessible and understandable to the people at risk and to those responsible for minimizing risk (Siekevitz 1970).

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